*Kidney International, Vol. 57 (2000), 2511–2518*

# Renal blood flow measurement by positron emission tomography using $^{15}O$-labeled water

**Laurent Juillard, Marc F. Janier, Denis Fouque, Martine Lionnet, Didier Le Bars, Luc Cinotti, Paul Barthez, Claude Gharib, and Maurice Laville**

*Département de Néphrologie, Hôpital Edouard Herriot, Lyon; Centre d'Exploration et de Recherche Médicale par Emission de Positons (CERMEP), Hôpital Cardiologique, Bron; Ecole Nationale Vetérinaire de Lyon, Marcy l'Etoile; and Equipe Accueil EA 645, Université Claude Bernard, Lyon, France*

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*Background.* Only few noninvasive methods have the potential to quantitate renal blood flow (RBF) in humans. Positron emission tomography (PET) is a clinical imaging method that can be used to measure the tissue blood flow noninvasively. The purpose of this study was to validate PET measurement of RBF using $^{15}O$-labeled water ($H_2{}^{15}O$), a tracer that allows repeated measurements at short time intervals.

*Methods.* RBF was measured in six pigs by PET and by radioactive microspheres (MS). Three measurements were performed in each pig at baseline (BL), during vascular expansion and dopamine infusion (DA; 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intravenously), and during angiotensin II (Ang II) infusion (50 ng $\cdot kg^{-1} \cdot min^{-1}$ intravenously). RBF was estimated from aortic and renal tracer kinetics using a model adapted from the blood flow model described by Kety and Smith.

*Results.* PET and MS values correlated strongly ($y = 0.79x + 42$, $r = 0.93$, $P < 0.0001$) over the RBF range from 100 to 500 $mL \cdot min^{-1} \cdot 100\ g^{-1}$. Pharmacologically induced changes were significant and were measured equally well by PET and MS: 38 and 39%, respectively, below BL ($P < 0.005$ and $P < 0.05$) under Ang II, and 47 and 48%, respectively, above BL ($P < 0.005$ and $P < 0.01$) under DA. A Bland and Altman representation showed a low average difference of $-17 \pm 45\ mL \cdot min^{-1} \cdot 100\ g^{-1}$ (mean $\pm$ SD).

*Conclusion.* To our knowledge, this study provides the first validation of RBF measurement by PET using $H_2{}^{15}O$ over a large range of RBF values (100 to 500 $mL \cdot min^{-1} \cdot 100\ g^{-1}$), which correspond to RBF values in both healthy subjects and in patients suffering from chronic renal failure.

Determination of renal blood flow (RBF) is useful in both clinical and experimental circumstances to evaluate vascular damage to the kidney caused by renal artery stenosis, renal vasculitis, chronic allograft rejection, and nephrotoxic drugs.

In clinical practice, RBF can be estimated indirectly by para-aminohippuric acid (PAH) clearance, corrected for hematocrit and possibly PAH extraction. These corrections impair the accuracy of RBF measurement and make it unsuitable in cases of chronic renal insufficiency. Moreover, PAH clearance provides only a two-kidney value of RBF and cannot be repeated more often than in 30-minute periods. These limitations have stimulated research for a method that would allow direct measurement of RBF, with the ability to record regional renal perfusion every 10 minutes. Other functional imaging tools, magnetic resonance imaging with arterial spin tagging [1, 2], and electron beam computed tomography [3], have been shown to noninvasively measure RBF.

Positron emission tomography (PET) is a noninvasive tool routinely used in humans to quantitatively measure myocardial and cerebral blood flow. This technique has been validated against the radioactive microspheres (MS) method for quantitative measurement of myocardial and cerebral blood flow using a one-compartment model [4, 5].

Few studies have adapted PET to measure RBF [6–9] using oxygen 15-labeled water ($H_2{}^{15}O$) and nitrogen 13-labeled ammonia ($^{13}NH_3$). Although both tracers can be used, $H_2{}^{15}O$ appears to be more suitable because its shorter half-life (2 vs. 11 min) allows measurements at shorter time intervals (15 vs. 60 min). $H_2{}^{15}O$ is diffusable and, compared with ammonia, is neither extracted nor metabolized in the kidney. $H_2{}^{15}O$ kinetics can be described by a simple monocompartmental model, which is more accurate for high flows typically measured in the kidney [10]. These benefits are counterbalanced by a lower spatial resolution with $H_2{}^{15}O$ compared with $^{13}NH_3$. To date, however, despite the potential benefits of renal hemodynamic studies, RBF measurement by PET using $H_2{}^{15}O$ has never been validated. The aim of this study

**Key words:** renal circulation, kidney blood flow, microspheres, oxygen 15-labeled water, noninvasive measurement, PET.

Received for publication August 24, 1999
and in revised form December 17, 1999
Accepted for publication January 20, 2000

was to validate measurements of RBF by PET using $H_2{}^{15}O$ against the MS reference method.

## METHODS

### Animals

This study design was in compliance with the guidelines for the care and use of laboratory animals as described by the National Institutes of Health.

This study was performed on six four-month-old farm pigs (average body weight 27.9 ± 2.1 kg, mean ± SD). Pigs were sedated before general anesthesia using 25 mg of droperidol, 3 mg of xylazine (4%), and 10 mg of ketamine by intramuscular injection. Anesthetic induction was achieved using propofol, 2 mg/kg intravenously, followed by 0.5 mg/min continuous perfusion. Animals underwent a tracheostomy and were mechanically ventilated. Before surgery, aortic diameter and renal cortex thickness were measured using ultrasonography (EUB-25; Hitachi®, Tokyo, Japan). An 8 F catheter was inserted into the right internal carotid for arterial blood sampling and mean arterial pressure (MAP) recording. A dual lumen catheter was inserted in the right internal jugular vein for fluid and drug infusion. A pigtail catheter was placed in the left atrium through a short left thoracotomy for MS infusion. Animals were transported to the PET scan room and were then anesthetized with fluothane (0.7%) to insure constant central hemodynamics. Animals were placed in right lateral recumbence within the PET scanner.

### Sequence of vasoactive drug infusion and hemodynamic measurement

Renal blood flow was measured three times in each pig with both PET and MS: (*1*) baseline (BL), after 20 minutes of rest, and under two different pharmacological stimulations at 30-minute intervals; (*2*) during a continuous infusion of dopamine 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ associated with vascular expansion by hydroxyethylstarch (Elohes®, Fresenius®, Sevres, France) and isotonic saline (DA); and (*3*) during a continuous infusion of angiotensin II (Ang II) 50 $ng \cdot kg^{-1}min^{-1}$. Dopamine-expected effects were an increase in cardiac output and renal vasodilation resulting in an increase of RBF. Ang II-expected effects were a strong systemic and renal vasoconstriction resulting in a decrease of RBF. These pharmacological stimulations were designed to obtain and observe a large range of RBF values. Once a stable mean arterial blood pressure was achieved in each condition, $H_2{}^{15}O$ was injected. At the end of the PET acquisition (total scan time of 3 min), MS were injected.

### RBF measurements with radioactive microspheres

The RBF measurement with MS was performed as previously described [11]. Fifteen micrometers of MS, labeled with $^{141}$cerium, $^{103}$ruthenium, and $^{95}$niobium suspended in isotonic salt solution with 2% Tween 80 (NEN®, Dupont de Nemours®, Boston, MA, USA) were used. An aspirating pump began 30 seconds before and stopped 50 seconds after a bolus injection of MS to ensure constant sampling flow. About $10^6$ MS were injected successively after sonication and suspended in 10 mL of isotonic saline.

After the last measurement, animals were sacrificed. Renal vascular pedicles were ligated. Kidneys were removed, and 10 pieces of approximately 3 g of cortex were excised from each kidney. The activity of cortex samples was then measured in a calibrated counter (Auto Gamma®, Cobra II®; Packard, Downers Grove, IL, USA).

### PET measurements

For each PET measurement, 260 MBq of $H_2{}^{15}O$ were injected intravenously at a constant rate over 20 seconds. Starting simultaneously, a dynamic series of images was acquired using a CTI/Siemens HR + PET scan [12], with an average plane resolution of 8 mm for $H_2{}^{15}O$. Each series was composed of eight 4-second images, four 6-second images, six 10-second images, and four 20-second images (total 22 images). Photon attenuation was corrected using a transmission scan obtained with a germanium source. Images were reconstructed using a filtered back projection method with a frequency cut-off of 0.3 $mm^{-1}$. For each slice, a static image was generated by summation of all 22 dynamic images (Fig. 1).

A region of interest (ROI) was drawn automatically around the aorta on static images as a line limited by 80% of the maximum activity for the aorta. ROIs were drawn manually around the renal cortex on static images. Time activity curves (TACs) were generated for the aorta and each renal cortex (Fig. 2). The Mediman software was used for ROIs drawing and TAC computation [13].

Renal blood flow, delay between aortic and kidney invasion by $H_2{}^{15}O$ ($\delta$), and vascular fraction in the kidney (VF) were fitted (details of modeling appear in the **Appendix**). Partial volume correction factors on kidney (Fkk) and aorta (Fbb) were set at 1, since the aortic diameter and renal thickness were similar. The tissue/blood partition coefficient ($\rho$) was set at 1, as the ratio between the proportion of water contained in blood (0.83) [14] and kidney (0.81) [15].

Time-activity curves used as input and tissue functions were averaged (weighted by the number of pixels in ROI) from TACs obtained by ROIs traced on the slices of interest for the aorta (about 10 slices) and on both kidney cortices (about 6 planes), respectively.

Fitting was performed with a custom program using the nonlinear regression module of Matlab® software (Mathwork Inc.®, Natick, MA, USA). Fitting quality was evaluated by standard deviation of fitted parameters

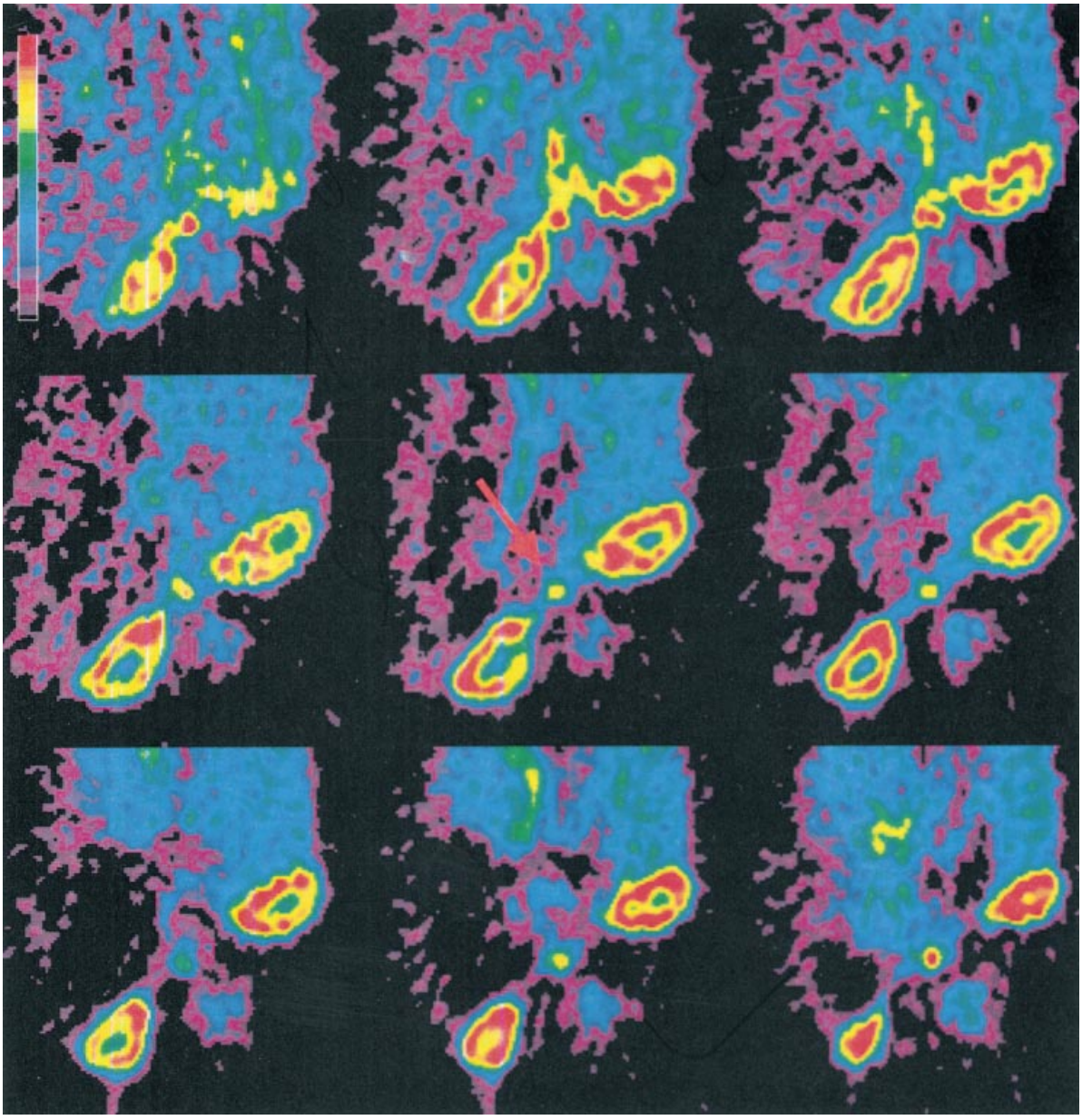

**Fig. 1. Renal positron emission tomography (PET) static images using $H_2{}^{15}O$ in pigs.** Each image represents a transverse slice (0.97 cm thick) where the kidneys and the aorta (arrow on central image) are displayed. (Orientation: Ant = up, Right = left. The upper left image represents the subdiaphragm slice, and the lower right image represents the inferior slice). Reproduction of this figure in color was made possible by SA Ezus-Lyon 1, Villeurbanne, France.

calculated with the local gradient matrix of fitted parameters.

### Calculations and statistics

Renal vascular resistances (RVR, mm Hg · $mL^{-1}$ · min · 1100 g) were estimated as the ratio of MAP (mm Hg) to RBF measured with PET (mL · $min^{-1}$ · 100 $g^{-1}$). Changes in RBF, MAP, and RVR under pharmacological interventions were analyzed with an analysis of variance factorial model and Fisher post hoc test to compare couples of the three measures. The comparison between PET and MS estimations of RBF was performed by the Wilcoxon nonparametric test.

Measurements from all regions of the two kidneys were averaged for PET and MS measurements, respectively, in order to avoid redundancy in the comparison. An agreement between the two methods was determined using a linear correlation between RBF measurements obtained by PET and MS and by the representation described by Bland and Altman [16]. For both kidneys

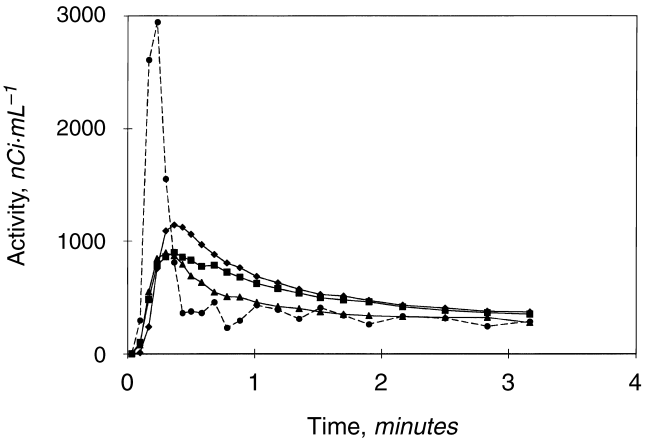


**Fig. 2. Examples of aortic (●, dashed line) and tissue (solid lines) PET time-activity curves from one pig.** Input function (aortic PET time-activity curve) represents the evolution in time of the mean of activity (nCi/mL) measured in the aortic region of interest (ROI). Tissue function (kidney PET time-activity curves) represents the evolution in time of the mean of activity (nCi/mL) measured in the kidney ROI, during baseline (BL; ◆), dopamine infusion (▲), and angiotensin II (Ang II) infusion (■).

**Table 1.** Results at baseline, and under dopamine (DA) or angiotensin II (Ang II) infusion

| Stimulations | Baseline | DA | Ang II |
|---|---|---|---|
| MAP *mm Hg* | 78 ± 10 | 84 ± 12 | 99 ± 7[b] |
| RVR | | | |
| *mm Hg · mL⁻¹ · min · 100 g⁻¹* | 0.29 ± 0.08 | 0.20 ± 0.02 | 0.62 ± 0.27[b] |
| MS-RBF | | | |
| *mL · min⁻¹ · 100 g⁻¹* | 270 ± 88 | 401 ± 83[a] | 163 ± 63[a] |
| PET-RBF | | | |
| *mL · min⁻¹ · 100 g⁻¹* | 253 ± 73 | 372 ± 40[b] | 158 ± 38[a] |
| VF % | 0.090 ± 0.073 | 0.082 ± 0.044 | 0.070 ± 0.0127 |
| δ *seconds* | 3.9 ± 1.8 | 3.2 ± 1.0 | 2.3 ± 4.2 |

Abbreviations are: MAP, mean arterial pressure; RVR, renal vascular resistance; RBF, renal blood flow measured by MS and PET; VF, vascular fraction; δ, delay.
[a]$P < 0.05$ and [b]$P < 0.005$ vs. baseline

in each pig, the coefficient of variation (CV; standard deviation of regional measurements/mean of regional measurements) was calculated for MS and PET regional RBF measurements.

Differences were considered significant if $P < 0.05$. Statistical analysis was done using the Statview® software program (Abacus Concepts®, Berkeley, CA, USA).

## RESULTS

The baseline MAP (Table 1) was 78 ± 10 mm Hg. MAP was not raised significantly by DA ($P = 0.31$) but was increased significantly by Ang II ($P < 0.005$). Baseline RVR values were 0.29 ± 0.08 mm Hg · mL$^{-1}$ · min · 100 g (Table 1). RVR was not lowered significantly by dopamine ($P = 0.25$) and was increased significantly by Ang II ($P < 0.005$).

**Table 2.** Coefficient of variation in the three study conditions

| | | Coefficient of variation | | | |
|---|---|---|---|---|---|
| | | MS-RBF | | PET-RBF | |
| Pig # | Condition | Left | Right | Left | Right |
| 1 | Baseline | 0.33 (10) | 0.27 (10) | 0.04 (8) | 0.08 (7) |
| | DA | 0.32 (10) | 0.26 (10) | 0.08 (8) | 0.17 (8) |
| | Ang II | 0.32 (10) | 0.27 (10) | 0.03 (8) | 0.08 (7) |
| 2 | Baseline | 0.03 (10) | 0.04 (10) | 0.08 (7) | 0.06 (9) |
| | DA | 0.02 (10) | 0.04 (10) | 0.09 (7) | 0.17 (8) |
| | Ang II | 0.02 (10) | 0.03 (10) | 0.08 (8) | 0.09 (9) |
| 3 | Baseline | 0.04 (10) | 0.04 (10) | 0.09 (8) | 0.07 (8) |
| | DA | 0.02 (10) | 0.04 (10) | 0.11 (6) | 0.08 (7) |
| | Ang II | 0.06 (10) | 0.05 (10) | 0.07 (8) | 0.13 (7) |
| 4 | Baseline | 0.06 (10) | 0.04 (10) | 0.03 (6) | 0.02 (6) |
| | DA | 0.06 (10) | 0.03 (10) | 0.05 (6) | 0.08 (7) |
| | Ang II | 0.05 (10) | 0.03 (10) | 0.05 (7) | 0.05 (7) |
| 5 | Baseline | 0.03 (10) | 0.06 (10) | 0.08 (7) | 0.06 (7) |
| | DA | 0.03 (10) | 0.05 (10) | 0.08 (6) | 0.10 (7) |
| | Ang II | 0.03 (10) | 0.06 (10) | 0.05 (7) | 0.06 (7) |
| 6 | Baseline | 0.10 (10) | 0.04 (10) | 0.11 (7) | 0.09 (7) |
| | DA | 0.11 (10) | 0.04 (10) | 0.08 (8) | 0.04 (8) |
| | Ang II | 0.10 (10) | 0.05 (10) | 0.16 (8) | 0.16 (8) |
| Mean ± SD | | 0.09 ± 0.10 | | 0.08 ± 0.04 | |

Coefficient of variation (standard deviation of regional measurements/mean of regional measurements) of renal blood flow was measured by microspheres (MS-RBF) and by PET (PET-RBF) in the left and right kidneys in the three stimulation conditions (DA, dopamine; Ang II, angiotensin II). The number of regions are in parentheses.

The average aortic diameter was 10.1 ± 1.3 mm, and the average renal cortex thickness was 9.8 ± 1.6 mm. All 18 RBF values obtained by PET and MS were included in the statistical analysis.

Renal blood flow values using MS (MS-RBF) ranged from 111 to 511 mL · min$^{-1}$ · 100 g$^{-1}$. Baseline MS-RBF was 270 ± 88 mL · min$^{-1}$ · 100 g$^{-1}$ (Table 1). Vascular expansion and DA significantly increased MS-RBF (48% vs. BL, $P < 0.01$), and Ang II significantly decreased MS-RBF (−39% vs. BL, $P < 0.05$). Except in one pig (pig 1), regional RBFs measured by MS were homogenous (CV ranged from 2 to 33%, 8.8 ± 9.6%; Table 2).

Renal blood flow measured by PET using $H_2^{15}O$ (PET-RBF) ranged from 92 to 416 mL · min$^{-1}$ · 100 g$^{-1}$. BL PET-RBF (Table 1) was 253 ± 73 mL · min$^{-1}$ · 100 g$^{-1}$. Vascular expansion and DA significantly increased PET-RBF (38% vs. BL, $P < 0.002$), and Ang II significantly decreased PET-RBF (−38% vs. BL, $P < 0.01$). There was no significant variation of VF and δ under pharmacological stimulations (Table 1). Renal regional blood flows measured by PET were also homogenous (CV ranged from 2 to 17%, 8.1 ± 3.8%; Table 2).

Renal blood flow measurements performed by PET or MS were not significantly different when including all 18 measurements or in each pharmacologic condition. RBF measurements by PET and MS correlated strongly ($r = 0.93$, $P < 0.0001$; Fig. 3) with a slope of 0.79 and a nonsignificantly different from 0 intercept (42 mL · min$^{-1}$ · 100 g$^{-1}$, $P = 0.09$). The average difference between PET-

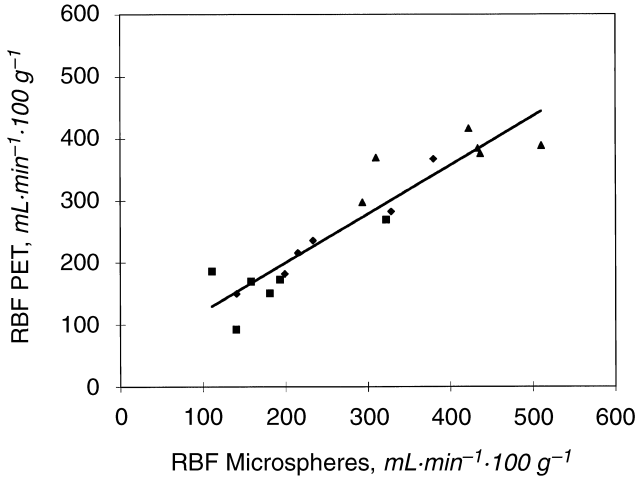


**Fig. 3. Correlation between RBF (mL · min · 100 $g^{-1}$) measured by PET using $H_2{}^{15}O$ and RBF (mL · min · 100 $g^{-1}$) measured by ratioactive microspheres (MS) during BL (◆), dopamine infusion (▲), and Ang II infusion (■; $y = 0.79.x + 42$, $r = 0.93$, $P < 0.001$, $N = 18$).**

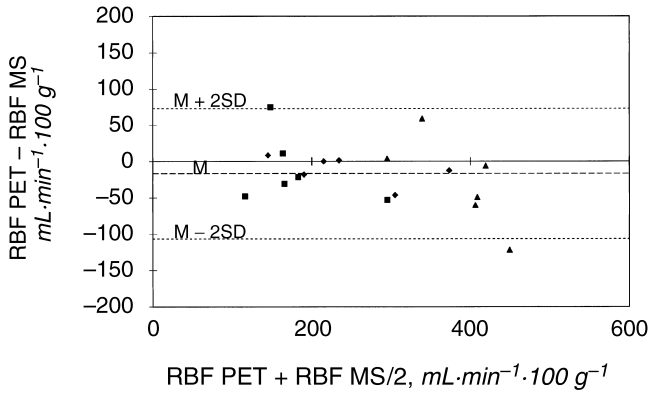


**Fig. 4. Bland and Altman representation of the agreement between RBF (mL · min · 100 $g^{-1}$) measured with PET using $H_2{}^{15}O$ and with MS during BL (◆), dopamine infusion (▲), and Ang II infusion (■).** The mean difference is −17 mL · min · 100 $g^{-1}$ (mean, dashed line) ± 90 mL · min · 100 $g^{-1}$ (mean ± 2 SD, dotted line).

RBF and MS-RBF was −17 mL · $min^{-1}$ · 100 $g^{-1}$ (6.3% of BL MS-RBF), and the standard deviation was 45 mL · min · 100 $g^{-1}$ (Fig. 4). No bias in the measurements was observed since a constant agreement was observed at all values of RBF (Fig. 4).

## DISCUSSION

This study demonstrates the ability of PET using $H_2{}^{15}O$ to measure acute changes accurately in RBF induced by pharmacologic stimulation compared with measurements with MS. The results showed a significant correlation between RBF measured by PET and RBF measured by MS, and a constant agreement between those two methods in a wide range of RBFs similar to those in humans. These results provide a strong rationale for using PET scans in human studies.

Until our study, measurements of RBF with PET using $H_2{}^{15}O$ have not been validated directly against the MS method. In normal volunteers, Nitzsche et al compared RBF measured by PET using $H_2{}^{15}O$ and $^{13}NH_3$ and found a good correlation between the two methods ($r = 0.91$) [9]. $^{13}NH_3$ is the unique PET-RBF measurement method validated experimentally using MS [10]. Inaba et al, who first used PET with $H_2{}^{15}O$ for measuring RBF in humans, justified the application of the Kety-Smith model solely on the observation of renal monoexponential clearance of radioactive water injected in renal arteries [6]. Kuten et al measured the effect of external irradiation on RBF with PET using $H_2{}^{15}O$ in five dogs by comparing relative variations in RBF between the PET and radioactive MS method [17]. A good agreement between these two methods was reported. However, the accuracy of this study was limited because of the lack of absolute PET-RBF measurement and few details about the method used for PET measurement.

The goal of this study was to validate a new method of RBF measurement compared with a reference method. Agreement is usually evaluated by assessing the correlation between the results of the two methods. We found a strong linear relationship in the present study. Similar correlations were observed in the validation of RBF measurement by PET with $^{13}N$-labeled ammonia ($r = 0.91$, slope at 1.06, intercept at 17 mL · min · 100 $g^{-1}$) [10] or myocardial blood flow measurement with $H_2{}^{15}O$ ($r = 0.89$, slope at 0.79, intercept at 13 mL · min · 100 $g^{-1}$) [4]. However, even when the correlation is significant, the slope should be close to 1 and the intercept null, corresponding to identity results, to provide strong arguments for agreement. Bland and Altman outlined the limitation of the use of correlation in this case because serial values are not statistically independent (that is, linked to the physiologic parameter measured) [16]. In this study, the Bland and Altman analysis (Fig. 4) showed good agreement with a low average difference (−17 mL · min · 100 $g^{-1}$) and an acceptable standard deviation (45 mL · min · 100 $g^{-1}$). The graphic representation clearly showed the absence of proportional bias between PET-RBF and MS-RBF, without increased differences at higher or lower flows, over a large range of RBF values (Fig. 4).

The correlation was found to be similar to other reported PET studies; however, these results are not ideal for three reasons. First, the study was based on a one-compartment model. The monocompartmental model initially described by Kety and Smith has been validated for the measurement of myocardial [4] and cerebral [5] blood flow by PET using $H_2{}^{15}O$ [18]. This model of diffusion is easily adapted to the heart and brain but is more questionable for the kidney, which involves a complex

fluid transfer system due to the glomerular filtration and tubular reabsorption processes. Glomerular filtration most likely influences the kinetics of $H_2^{15}O$ in the renal cortex by introducing a delay in the disappearance of vascular activity. However, adding new compartments in fitting may compromise an accurate estimation of each parameter. The choice of fitted or fixed parameters was strictly developed under mathematical constraints and was based on physiologic relevance. Model accuracy must be judged on the values of other fitted parameter values. An estimated vascular fraction (10%) has been found in the range of measured blood volume in literature [19]. There was no significant difference between VF measured under pharmacological stimulations. Estimated delays were also not significantly different under pharmacological stimulations and in the range of delay between aortic and tissular water invasion, as estimated visually on images.

Second, the limited resolution of PET scans induces error in external measurement of true activities [14]. Among these errors, the partial volume effect (PVE) corresponds to the loss of measured activity on a small size structure. The PVE results in underestimation of true activity depending on the ratio between the studied structure's size and the ROI size. Another potential source of error is the spillover effect (SOE) between two adjacent structures, which is quantitatively more important if structures are closer and have different activities. The evaluation of the PVE and the SOE is an important task for quantitation in PET. Without methods for correcting images or TACs from PVE, correction factors were set to 1, corresponding to absence of correction. Correction for the PVE would be required if aortic and renal cortex size were different. However, preoperative ultrasonographic measurements indicated that aortic diameter and renal cortex thickness were similar in the pigs used in this study (averaged difference of 0.4 mm). Corrections for the PVE surely would improve correlation and reduce interindividual variability.

Third, the only method available for regional tissue perfusion model validation that allows repeated measurements at short intervals is the MS method. This simple method [11] can result in numerous technical failures [20–23]. The choice of MS size is a compromise between good statistical counting obtained with small MS and good trapping of large MS in capillaries. For RBF measurements, the optimal size is 15 μm [22]. However, this method does not provide accuracy of each measurement, and this point could partially explain the difficulty of obtaining perfect correlation in this study.

Renal blood flow changes under Ang II were greater than previously published data that showed a 25% decrease [24, 25]. Under dopamine infusion, RBF increased more than expected (approximately 25%) [25–27]. This fact may be due to associated volume expansion, which is an important factor of RBF increase. On the other hand, as expected, MAP was not raised significantly (8%, $P = 0.31$) under dopamine [25, 27], but increased significantly [24, 25] under Ang II (27%, $P < 0.005$). As also expected, RVR increased dramatically under Ang II (113%, $P < 0.005$) and was not decreased significantly under dopamine (−31%, $P = 0.25$).

The choice of the animal model was crucial. Pig appeared well suited for RBF measurement performed in this study, and the animal's size allowed PET imaging of the aorta and kidney, the sizes of which are similar to human kidney. Pig kidneys are unlobulated and multipapillar, and are quite similar to human kidney architecture. Nevertheless, baseline RBF measured in pigs was found to be lower than RBF found in healthy humans. This difference can be explained by the age of pigs, because, as in humans [28], young pigs (until the age of one year) have immature kidneys with lower RBF values [29], even when corrected for body surface area. RBF values measured in the present study were similar to RBF measured by other investigators in young pigs (close to 200 mL · min · 100 $g^{-1}$) [30, 31]. In addition, anesthetic and surgical procedures may have reduced RBF. Under simple pharmacological stimulation, the present experimental model provides a fivefold increase in RBF, a wide range allowing us to use this model in a large field of physiological and pathological values. The highest RBF values measured in this study were close to normal human RBF values, and the range of RBF included RBF values observed in CRF patients.

Finally, this study does not emphasize one of the major applications for measuring RBF with PET, that is, regional RBF evaluation. We chose to use the entire renal cortex and to average both kidney RBFs for statistical reasons. Using dependent data would have artificially improved the agreement between the two RBF measurement methods. Poulsen et al described a heterogeneity in RBF distribution in swine kidney. In our study, except in one pig (pig 1), regional blood flows measured by MS were homogenous (CV ranged from 2 to 33%, 8.8 ± 9.6%) [30]. PET measurements were also homogenous (CV ranged from 2 to 17%, 8.1 ± 3.8%). Even if the regional perfusion localization of measurement by PET and MS was not strictly identical, there was no detectable difference between the regional cortical RBF, as measured by the two methods (Table 2).

In conclusion, PET using $H_2^{15}O$ is a valuable noninvasive method for measuring RBF. Limitations of the method include the cost of the procedure and the lack of availability of PET facilities. Advantages of RBF evaluation by PET include the possibility of sequential measures at short intervals (as performed in this study), a comparison between measures performed at long intervals, because RBF measurements are absolute, and reduced irradiation to the patient.

## ACKNOWLEDGMENTS

This study was supported by grants from Parke Davis Corp., the Hospices Civils de Lyon, and University Claude Bernard Lyon 1. We thank Prof. D. Comar and Prof. J.F. Pujol, CERMEP Directors. We are indebted to Emanuelle Canet, Gérard Galy, Véronique Berthier, Franck Lavenne, Christian Pierre, Laurent Veyre, and Fréderic Bonnefoi for pertinent advice and technical assistance. Reproduction of Fig. 1 in color was made possible by SA Ezus-Lyon 1, Villeurbane, France.

*Reprint requests to Laurent Juillard, M.D., Hôpital Edouard Herriot, Pavillon P, 3 place D'Arsonval, 69437 Lyon Cedex 03, France. E-mail: laurent.juillard@chu-lyon.fr*

## APPENDIX

The theoretical model for measuring blood flow is described by Kety-Smith [18].

The following differential equation describes the rate of change of $H_2{}^{15}O$ in the tissue compartment:

$$\frac{dCt}{dt} = \frac{RBF}{V}Ca - \frac{RBF}{\rho V}Ct \qquad \text{(Eq. 1)}$$

where Ct and Ca are $H_2{}^{15}O$ activities in counts · pixel · $min^{-1}$ measured in the ROIs in the renal cortex and the aorta, V is the distribution volume in renal tissue within the ROI (mL). The constant ($\rho$) is the tissue/blood partition coefficient (water contained in blood/water contained in kidney mL/g). From equation 1,

$$Ct(t) = Ca(t) * \rho k e^{-kt} \qquad (k = RBF/\rho V) \qquad \text{(Eq. 2)}$$

where the asterisk indicates a convolution integral. When integrating both sides of equation 2 for the scan time duration, we obtain the following:

$$\int_{t_i}^{t_{i+1}} Ct(t)dt = \int_{t_i}^{t_{i+1}} Ca(t) * \rho k e^{-kt} dt \qquad (k = RBF/\rho V) \quad \text{(Eq. 3)}$$

The left part of the equation is calculated from data obtained on kidney cortex TAC (Ct), and the right side is calculated with the aortic TAC (Ca).

### Practical use of the model and simulation experiments

The Kety-Smith model [18] must be adapted to PET by including variation in Ca and Ct induced by resolution limitation (the PVE and the SOE) [14, 32].

Activities measured by PET Ct′ on kidney cortex and Ca′ on the aorta are then:

$$Ct' = Fkk \cdot Ct + (Fbk + VF) \cdot Ca$$

$$Ca' = Fbb \cdot Ca + Fkb \cdot Ct$$

where Fkk (kidney) and Fbb (blood) are, respectively, correction factors of PVE on renal cortex and the aorta. Fkb represents the renal cortex spillover on the aorta, Fbk the aorta spillover on renal cortex, and VF the vascular fraction (blood volume in the renal cortex in which activity in not tissular diffusion). No SOE between the aorta and the kidneys was considered because the distance between the aorta and the kidneys was always greater than maximum distance path of the positron in water (6 mm). The vascular fraction can be measured either directly by PET with $^{15}O$-labeled carbon monoxide with correction for vascular activity of the renal TAC before modeling [6] or by introducing VF in the model as a new parameter [10]. The second simpler approach was chosen. The delay ($\delta$) between the tracer arrival at the input function and the tissue function sites of measurement is another important parameter.

Six parameters (F/V, $\rho$, $\delta$, Fkk, Fbb, and VF) are then included in the Kety-Smith model adapted for PET (equation 4):

$$C_{TEP}(t) = \frac{1}{t_{i+1} - t_i} \int_{t_i}^{t_{i+1}} Ct'(t).dt$$

$$= \frac{1}{t^i{}_{+1} - t^i} \cdot \frac{Fkk}{Fbb} \left(\int_{t_i}^{t_{i+1}} Ca'(t + \delta)\right)$$

$$* \rho k e^{-kt} + \frac{VF}{Fkk} \cdot Ca'\ (t + \delta)).dt) \qquad \text{(Eq. 4)}$$

Information derived from aortic and tissue TACs does not allow fitting six parameters using nonlinear regression methods with relevant and reliable accuracy. This restriction imposes a selection of parameters for fitting and setting other parameters.

In a preliminary phase of modeling, simulation experiments were performed to study the interactions between parameters and parameter variation effects on RBF estimation. Artificial aortic and tissue TACs were created and calculated with combined known parameter values. The model was used to study variations of estimated RBF. Simulations led us to set Fkk, Fbb, and constant $\rho$ as interdependent factors that affected RBF estimation linearly. Variations of those three factors resulted in proportional errors without distortion at extreme flows. By contrast, simulation demonstrated that delay ($\delta$) and VF affected the estimation of RBF nonlinearly and had to be fitted in the model. In addition, those two parameters could be modified under a vasoactive drug during the experiments, VF as a consequence of cortex blood volume variations and the delay as a consequence of cardiac output variations induced by drugs.

Therefore, RBF, $\delta$, and VF were fitted with Fkk and Fbb set at 1 (approximation justified by a similar aortic diameter and renal thickness) and $\rho$ set at 1 as the ratio of 0.83 (water contained in blood) [14] over 0.81 (water contained in kidney) [15].

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